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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,099	01/20/2004	Timothy J. O'Leary	AFIP 03-16 01	4916

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OFFICE OF THE STAFF JUDGE ADVOCATE
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EXAMINER	
CALAMITA, HEATHER	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,099	O'LEARY ET AL.	
	Examiner	Art Unit	
	Heather G. Calamita, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *1-3 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. Claims 1-15 are currently pending. Claims 1-3 and 15 are withdrawn as being directed to non-elected subject matter. Claims 4-14 are under examination. All arguments have been fully considered and thoroughly reviewed, but are deemed not persuasive for the reasons that follow. Any objections and rejections not reiterated below are hereby withdrawn.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 4-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (Anal. Chem., 2000, cited in the IDS) in view of Wu et al. (Letters in Applied Microbiology, 2001, cited in the IDS).

With regard to claim 4, Singh et al. teach a method for immunoliposome assay comprising

a) encapsulating a markers within the liposomal bilayers (see p. 6020 col. 1 lines 16-18 and p. 6021 Figure 2)

b) associating selected receptors to the liposomal bilayers (see p. 6020 col. 1 lines 8-14 and p. 6021 Figure 2)

c) exposing the selected receptors to target analytes which bind to the liposomal bilayer associated selected receptors (see p. 6021 Figure 2, where the target analyte is the toxin)

d) removing unbound liposomal bilayers (see p. 6022 col. 1 under Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins, lines 14-18)

e) lysing the bound liposomal bilayers to release the markers (see p. 6022 col. 1 under Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins, lines 18-20)

g) detecting the markers (see p. 6022 col. 1 under Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins, lines 20-23)

With regard to claim 5, Singh et al. teach the target analytes are antigen and further comprising the step of immobilizing the target antigens on a substrate (see p. 6022 col. 1 under Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins, lines 1-7)

With regard to claim 6, Singh et al. teach the substrate is a microtiter plate and the receptors are antibodies specific to the immobilized target antigen (see p. 6022 col. 1 under Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins, lines 1-7)

With regard to claim 7, Singh et al. teach further comprising indirectly binding the analyte to the substrate (see p. 6022 col. 1 under Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins, lines 1-7).

With regard to claim 8, Singh et al. teach the receptors are gangliosides incorporated into the liposomal bilayer and the analyte is an antigen (see p. 6020 col. 1 lines 8-14 and p. 6021 Figure 2)

With regard to claim 10, Singh et al. teach the step of quantifying the amount of analyte present (see p. 6022 col. 1 under Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins, lines 20-23, where the amount of fluorescence correlates with the amount of analyte)

With regard to claim 11, Singh et al. teach the analyte is a biological toxin (see p. 6022 col. 1 under Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins, lines 1-7)

With regard to claim 12, Singh et al. teach an immunoliposome assay method comprising

a) selecting a substrate having primary antibodies attached thereto (see p. 6022 col. 1 under Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins, lines 1-23)

b) exposing the substrate to a target analyte containing sample (see p. 6022 col. 1 under Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins, lines 1-23)

c) permitting the target analyte to bind to the primary antibodies attached to the substrate (see p. 6022 col. 1 under Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins, lines 1-23)

d) removing all unbound analyte (see)

e) exposing the bound analyte to immunoliposomes where the immunoliposomes couple with the analyte (see p. 6022 col. 1 under Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins, lines 1-23)

f) removing any uncoupled immunoliposomes (see p. 6022 col. 1 under Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins, lines 1-23)

g) rupturing the coupled immunoliposomes to release the markers (see p. 6022 col. 1 under Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins, lines 1-23)

i) detecting the markers representative of the target analyte (see p. 6022 col. 1 under Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins, lines 1-23)

With regard to claim 13, Singh et al. teach the steps of attaching the primary antibodies to the substrate and removing all unattached primary antibodies (see p. 6022 col. 1 under Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins, lines 1-7).

With regard to claim 14, Singh et al. teach the analyte is a biotoxin where the immunoliposomes are ruptured using detergent and the markers are quantified (see p. 6022 col. 1 under Fluoroimmunoassay for Tetanus, Botulinum and Cholera Toxins, lines 18-23, where the detergent is Triton X-100 and the fluorescence is quantified).

Singh et al. do not teach all of the limitations of claims 4-14, specifically with regard to claim 4, Singh do not teach step a) encapsulating a plurality of identical nucleic acid segments within the liposome step f) subsequently amplifying the nucleic acid segments and step g) detecting the released nucleic acids.

With regard to claim 9, Singh do not teach the nucleic acid segments are amplicons that are amplified using PCR.

With regard to claim 12, Singh do not teach step e) the immunoliposomes contain amplicons, step g) releasing the amplicons form the immunoliposomes and step h) amplifying the amplicon population using PCR.

With regard to claim 14, Singh do not teach the quantifying the amplicons by gel electrophoresis.

With regard to claim 4 step a), Wu et al. teach using nucleic acids as reporters for amplification, f) amplifying the nucleic acids and g) detecting the nucleic acids as an indication of the presence of the analyte (see p. 322 col. 2 under Immuno-PCR assay lines 9-28 and p. 323 Figure 1).

With regard to claim 9, Wu et al. teach the nucleic acids are amplified using PCR (see p. 322 col. 2 under Immuno-PCR assay lines 9-28).

With regard to claim 12, Wu et al. teach e) and g) using nuclei acids as reporters and h) amplifying the nucleic acid reporters using PCR (see p. 322 col. 2 under Immuno-PCR assay lines 9-28).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. in order to detect the presence of an analyte in a sample with greater sensitivity than possible with standard immunoassay and fluorescence detection methods. Wu et al. state, "...the method described here demonstrates that immuno-PCR technology greatly extends the sensitivity of immunoassays. This hybrid technology exhibited analyte detection from 100 to 1000 fold better than the ELISA method performed with the same antibodies. Immuno-PCR technology, in principle, provides the basis for a new generation of sensitive immunoassays and may be useful in clinicopathological assays as

well as detection of low level antigens (see p. 325 col. 1 first full paragraph)." An ordinary practitioner would have been motivated to substitute the markers in the immunoliposome assay as taught by Singh et al. with nucleic acid reporters, as taught by Wu et al. in order to improve the sensitivity of the immunoliposome assay. The DNA reporters disclosed by Wu enable detection of analytes present in a sample at very low levels because the DNA markers improve sensitivity from 100 fold to 1000 fold over standard immunoassay methods, therefore the ordinary practitioner would expect a markedly higher degree of sensitivity in the immunoassay if the traditional fluorescence markers were substituted with the DNA reporters.

Response to Arguments

3. Applicants' arguments filed January 2, 2007, have been fully considered but they are not persuasive.

With respect to the 103 (a) rejections, Applicants argue the method of immuno PCR cannot be combined with the method of Singh. Applicants argue the covalent attachment of reporters to antibodies would prevent amplification by PCR and consequently Wu does not teach reporter/amplicons being quantified by PCR This argument is not persuasive because Wu is not relied on to teach covalent attachment of antibodies to reporter nucleic acids, but rather Wu is relied on for the principle of nucleic acid based antigen detection. In immuno PCR you bind the receptor to the target analyte to which DNA is bound. The difference is the intermediate step of DNAs bound to liposomes. Singh teaches using a liposome with gangliosides as receptors for biological toxins. Singh teaches the use of liposomes filled with fluorescent molecules which have gangliosides present in the liposomes. The toxin is captures using a Mab and then exposed to the ganglioside bearing liposoime. The liposomes having the fluorescent molecules provide a detection signal for each binding event. The concept of a nucleic acid reporter to replace the fluorescent reporter is very compatible with the method of Singh and Wu provide motivation to

use a nucleic acid reporter. As outlined in the rejection above Wu et al. state, "...the method described here demonstrates that immuno-PCR technology greatly extends the sensitivity of immunoassays. This hybrid technology exhibited analyte detection from 100 to 1000 fold better than the ELISA method performed with the same antibodies. Immuno-PCR technology, in principle, provides the basis for a new generation of sensitive immunoassays and may be useful in clinicopathological assays as well as detection of low level antigens (see p. 325 col. 1 first full paragraph)."

Applicants additionally, seem to argue at the bottom of p. 4 through p. 8 this is an "obvious to try" situation. The legal standard for "reasonable expectation of success" is provided by caselaw and is summarized in MPEP 2144.08, which notes "obviousness does not require absolute predictability, only a reasonable expectation of success; i.e., a reasonable expectation of obtaining similar properties. See, e.g., In re O'Farrell , 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)." In this factual case, there is express suggestion in the prior art that nucleic acid based antigen detection is a superior detection method. There is further evidence as shown by Singh who discloses in the prior art a method for analyte detection using liposomes. This sufficient for a reasonable expectation of success. The MPEP cites In re O'Farrell, which notes regarding "obvious to try" at page 1682, that,

> "In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. E.g ., In re Geiger , 815 F.2d at 688, 2 USPQ2d at 1278; Novo Industri A/S v. Travenol Laboratories, Inc ., 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); In re Yates , 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); In re Antonie , 559 F.2d at 621, 195 USPQ at 8-9. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. In re Dow Chemical Co ., 837 F.2d, 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1985); Hybritech, Inc. v. Monoclonal Antibodies, Inc ., 802 F.2d

1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1 986), cert. denied , 107 S.Ct. 1606 (1987);
In re Tomlinson ; 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966).

The court in O'Farrell then, affirming the rejection, notes " Neither of these situations applies here." For the instant case, it is clear that neither situations applies here either. This is not a situation where the prior art suggests varying a variety of parameters, since the prior art directly points to the use of nucleic acid based antigen detection and analyte detection using liposomes. This is also not a situation where only general guidance was given. The prior art provides specific guidance directing the use of both a nucleic acid based detection system and a liposome based detection system.

Applicants then argue impermissible hindsight and that there is no evidence provided for the prima facie case. These arguments are not persuasive because evidence is provided; the evidence provided is in the form of the references. The references provide the motivation to combine the teachings as outlined in the rejection above. With respect to the argument of hindsight, this argument is not persuasive because it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

With respect to applicants submission of Exhibits 1-6, these exhibits do not overcome the obviousness rejections over the claims.

Conclusion

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH

shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 5:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at 571.272.0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number 571.273.8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to 571.272.0547.

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